SHORT REPORTS

Hypercalcaemia and angioimmunoblastic lymphadenopathy

Hypercalcaemia is a rare and potentially lethal complication of lymphoma,¹ but was not found in over 400 patients with angioimmunoblastic lymphadenopathy.² We describe a patient with angioimmunoblastic lymphadenopathy in whom the development of hypercalcaemia was associated with an aggressive histological and clinical transformation of the disease.

Case report

A 57-year-old woman presented in November 1978 with a two-month history of intermittent fever, an evanescent non-pruritic rash, loss of 10 kg, and generalised lymphadenopathy and hepatosplenomegaly. Haemoglobin concentration was 7.8 g/dl, white cell count $31.6 \times 10^9/l$ ($31\,600/mm^3$), and platelet count $142 \times 10^9/l$. Erythrocyte sedimentation rate was 102 mm in first hour (Westergren), and Coombs test result was positive. Cold agglutinin titre was over 1/1020, and serum immunoglobulin concentrations showed a raised IgM value (2.5 g/l). Blood urea, creatinine, electrolyte, calcium, and phosphate concentrations were normal, as was serum alkaline phosphatase activity. Lymph node biopsy showed findings consistent with angioimmunoblastic lymphadenopathy, with an infiltrate of immunoblasts and plasma cells amidst small-vessel proliferation and amorphous acidophilic interstitial material.

In January 1979 the patient complained of increasing lethargy and nocturnal sweats. Red cells treated with chromium-51 showed a half life of eight days (normal 26-30 days). Prednisolone 40 mg/day was initiated, and in early February she had an episode of haematemesis and melaena. Endoscopy showed multiple gastric and duodenal ulcers, which on biopsy showed the histological changes of a mucosal infiltrate, consisting of sheets of large pleomorphic lymphoid cells with pyroninophilic cytoplasm, consistent with immunoblastic sarcoma. She was noted to be hypercalcaemic, with a blood concentration of 3.5 mmol/l (14.0 mg/100 ml). The figure shows her subsequent clinical course. Despite forced saline diuresis and intermittent

Serum calcium concentrations and response to various treatments in patient with angioimmunoblastic lymphadenopathy. Conversion: SI to traditional units—Calcium: 1 mmol/l $\approx$ 4 mg/100 ml.

intravenous mithramycin (25 μ g/kg), clinically significant hypercalcaemia persisted with values of 3.5-3.8 mmol/l (14.0-15.0 mg/100 ml). In late February splenectomy was performed because of progressive organomegaly, with anaemia and thrombocytopenia. Histologically a lymph node obtained at laparotomy showed complete loss of normal architecture and replacement by sheets of large and medium-size cells with pyroninophilic cytoplasm and frequent mitotic figures. Sections of the spleen showed ill-defined confluent arrangement of similar cells, consistent with immunoblastic sarcoma. In early March combination chemotherapy (CHOP) with cyclophosphamide (750 mg/m²), vincristine (1.4 mg/m²), adriamycin (50 mg/m²), and prednisolone (60 mg/m²) on days 1 to 5 was initiated, and three days later the serum calcium concentration was normal. The chemotherapy was complicated by

profound pancytopenia and massive gastrointestinal haemorrhage, which persisted despite total gastrectomy. Postoperatively the patient developed anastomotic leakage with subphrenic abscesses, and she died in April.

Necropsy showed multiple intra-abdominal abscesses due to breakdown of surgical anastomoses. No evidence of gastrointestinal lymphoma was found, but retroperitoneal nodes were affected with immunoblastic sarcoma. Parathyroids and bony structure were considered normal.

Comment

This patient presented with typical clinical manifestation of angioimmunoblastic lymphadenopathy, with fever, weight loss, non-specific rash in the setting of progressive lymphadenopathy, and hepatosplenomegaly. Associated abnormal immune function was shown by a positive Coombs test result, high cold agglutinin titres, and a raised blood IgM value.² The uniqueness of her clinical course was that, firstly, the progression of angioimmunoblastic lymphadenopathy into malignant immunoblastic sarcoma³ was accompanied with clinically important hypercalcaemia and, secondly, this malignant lymphoma affected the gastrointestinal tract. Despite manoeuvres for malignant hypercalcaemia,⁴ her raised blood calcium concentrations persisted until the dissolution of tumour mass with combination chemotherapy. Tumour cytolysis, however, was complicated by massive gastrointestinal bleeding, which necessitated surgical intervention. The basis of hypercalcaemic angioimmunoblastic lymphadenopathy is obscure, but both parathyroid hormone and osteoclast stimulating factor production have been described in haemopoietic neoplasms.⁵ In our patient the parathyroid hormone concentration was marginally raised at 1.8 μ g/l (normal <1 μ g/l) during the hypercalcaemia.

¹ Canellos GP. Hypercalcemia in malignant lymphoma and leukemia. *Ann NY Acad Sci* 1974;**230**:240-6.

² Pruzanski W. Lymphadenopathy associated with dysgammaglobulinemia. *Semin Hematol* 1980;**17**:44-62.

³ Nathwani BN, Rappaport H, Moran EM, Pangalis GA, Kim H. Malignant lymphoma arising in angio-immunoblastic lymphadenopathy. *Cancer* 1978;**41**:578-606.

⁴ Mazzaferri E, O'Dorisio TM, LoBuglio AG. Treatment of hypercalcemia associated with malignancy. *Semin Oncol* 1978;**5**:141-53.

⁵ Besarab A, Caro J. Mechanisms of hypercalcemia in malignancy. *Cancer* 1978;**41**:2276-85.

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Evidence for previous hepatitis B virus infection in alcoholic cirrhosis

Previous infection with hepatitis B virus can be detected by serological examination for antibodies to the hepatitis B surface antigen (anti-HBs) and core antigen (anti-HBc).¹ An initial study of the prevalence of serum anti-HBs in patients with chronic liver disease has indicated a particularly high prevalence of antibody in alcoholic cirrhosis.² A more extensive investigation is now reported.

Patients, methods, and results

Two hundred and fifty Caucasian patients with chronic liver disease proved histologically were examined prospectively. Full clinical particulars were recorded as before.² Portal hypertension was defined as the endoscopic or radiological demonstration of oesophageal varices. Details of occupation, previous blood transfusion, jaundice, tattoos, drug addiction, and needle

injections were documented. Control groups consisted of blood donors, hospital inpatients with cardiac and respiratory disease, and chronic alcoholics without liver disease.

Sera were examined for hepatitis B surface antigen (HBsAg), anti-HBc, and anti-HBs by radioimmunoassay (Ausria II, Corab, and Ausab, Abbott Laboratories) and reported as positive or negative compared with standard controls. Sera were also examined for antibodies to 12 common infective agents—namely, influenza A and B, adenovirus, *Mycoplasma pneumoniae*, psittacosis, *Coxiella burnetii*, herpes simplex, cytomegalovirus, varicella zoster, mumps, and measles by complement fixation test and rubella by haemagglutination-inhibition test. All sera were examined without knowledge of the clinical diagnosis. Statistical analysis was by χ^2 test and, where appropriate, by Fisher and Yates's exact test.

All sera gave negative test results for HBsAg. The positive hepatitis B virus antibody results are recorded in the table. Significant differences between patients and controls were confined to those patients with alcoholic cirrhosis. Hepatitis B virus antibodies were found in 28 (34%) of the 82 patients with alcoholic cirrhosis ($p < 0.0001$) and in 18 (47%) of the 38 with portal hypertension, 11 (44%) of the 25 who died within 6 months, 13 (42%) of the 31 with hepatic encephalopathy, and 13 (32%) of the 41 with ascites. Among patients with alcoholic cirrhosis hepatitis B virus antibodies were equally common in those whose liver biopsy appearances were diagnostic of active alcoholic liver disease (25 of the 73 patients) and in those with inactive cirrhosis (3 of the 9 patients). There was no significant difference between the patients with alcoholic cirrhosis and the remaining patients with liver disease in respect of previous blood transfusion, jaundice, the finding of tattoos, or social class, and no patients admitted to parenteral drug abuse. The distribution of hepatitis B virus antibodies between men (21 of the 56 patients) and women (7 of the 26 patients) with alcoholic cirrhosis was not significantly different.

There was no significant increase in the prevalence of antibodies to the 12 common infective agents in patients with alcoholic liver disease. In patients with chronic active hepatitis and cryptogenic cirrhosis, however, there was a significant rise in antibody titres to measles and the patients with cryptogenic cirrhosis also had raised antibody titres to rubella, observations which have previously been described.³

Comment

The high prevalence of serum antibodies to hepatitis B virus antigens in alcoholic cirrhosis has been confirmed in this survey and shown to be more common in advanced cirrhosis. Anti-HBc and anti-HBs were often both present, a response characteristic of previous hepatitis B virus infection.¹ The failure to show abnormal antibody titres against other common infective agents in alcoholic cirrhosis indicates the specificity of this response.

Factors which may be associated with an increased prevalence of serum hepatitis B virus antibodies are increasing age, male sex, foreign domicile, lower social class, exposure to infective serum, male homosexuality,⁴ and institutional life. Sexual histories were not taken from our patients but homosexuality would seem to be an unlikely explanation for our results. None of the above factors can explain our findings in alcoholic cirrhosis.

The incidence of liver disease among chronic alcoholics is variable. While the development of liver disease is related to both the volume of alcohol consumed and the duration of intake, the overall prevalence of cirrhosis in alcoholics remains between 10 and 15%.⁵ Other factors are therefore important. Host factors may determine susceptibility, as alcoholic hepatitis appears to develop more quickly in women, and alcoholic cirrhosis may be associated with HLA-B8.⁵ Nevertheless, other genetic or environmental factors, as yet unidentified, may also be important in the progression to chronic liver disease in the alcoholic. Previous hepatitis B virus infection could be such a risk factor, selecting a population of chronic alcoholics who are then susceptible

to alcohol-induced hepatic damage. More evidence, however, is required before establishing a pathogenic relation between the hepatitis B virus and chronic alcoholic liver disease.

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Androgens, oestrogens, and coronary heart disease

To test the hypothesis that testosterone may be a risk factor for coronary heart disease¹ we compared serum androgen and oestrogen concentrations in men with a history of myocardial infarction and in matched controls.

Patients, methods, and results

In a population-based case-control study 50 middle-aged men who had had a myocardial infarction five months to 11 years before (median 57 months) were each matched with a control man of the same age and marital state working in the same factory and known to be free of coronary heart disease.² Information on other coronary risk factors including cholesterol and blood pressure, weight, height, and smoking history were obtained from a recent screening examination.

Two blood samples were taken from each subject 15 minutes apart between 9 and 11 am and the serum frozen to -20°C on the same day. Measurements on pooled samples from the two venepunctures were made by radioimmunoassay using validated and published methods. At the time of the study 15 men were taking a beta-blocking drug (three together with clofibrate), 12 clofibrate (three in combination with beta-blockers), and four various other drugs.

The figure compares hormone concentrations according to drugs being taken with the concentrations in matched controls. The 12 men taking

Hepatitis B antibodies in patients with chronic liver disease and in controls

Group	Diagnosis	No of patients	No of women	Mean age (years)	No of patients with:			Total No (%) of patients with hepatitis B antibodies
					Anti-HBc alone	Anti-HBs alone	Both anti-HBc and anti-HBs	
1	Alcoholic steatosis	33	10	49	1	2	2	5 (15)
2	Alcoholic hepatitis	46	20	50	0	3	3	6 (13)
3	Alcoholic cirrhosis	44	16	55	0	2	8	10 (23)
4	Alcoholic cirrhosis and portal hypertension	38	10	56	1	5	12	18 (47)
5	Chronic alcoholism (no liver disease)	31	5	49	0	0	3	3 (10)
6	Primary biliary cirrhosis	34	32	57	0	1	5	6 (18)
7	Chronic active hepatitis	28	20	50	1	0	3	4 (14)
8	Cryptogenic cirrhosis	18	10	54	0	0	2	2 (11)
9	Haemochromatosis	19	0	52	0	0	0	0 (0)
10	Hospital inpatients, matched for 3 and 4	82	26	55	0	2	2	4 (5)
11	Blood donors, matched for 3 and 4	82	26	55	0	0	3	3 (4)
12	Hospital inpatients, matched for 6	34	32	57	0	1	2	3 (9)

Total hepatitis B virus antibodies: 3 v 10 $p < 0.005$; 4 v 10 $p < 0.0001$; 6 v 12 $p > 0.1$; 3 and 4 v 1 and 2 $p < 0.01$; 4 v 3 $p < 0.025$. Remainder (1, 2, 5, 7, 8, 9)—no significant difference from 10.